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Proteolytic processing of neuropeptide Y and peptide YY by dipeptidyl peptidase IV.

Mentlein R, Dahms P, Grandt D, Kruger R.

Anatomisches Institut, Universitat Kiel, Germany.

Neuropeptide Y, peptide YY and pancreatic polypeptide share an evolutionary conserved proline-rich N-terminal sequence, a structure generally known to be inert to the attack of common proteinases, but a potential target for specialized proline-specific aminopeptidases. Purified human dipeptidyl peptidase IV (also termed CD 26) liberated N-terminal Tyr-Pro from both, neuropeptide Y and peptide YY, with very high specific activities and Km values in the micromolar range, but almost no Ala-Pro from pancreatic polypeptide. Other proline-specific aminopeptidases exhibited low (aminopeptidase P, liberation of N-terminal Tyr) or totally no activity (dipeptidyl peptidase II), as was also observed with less-specific aminopeptidases (aminopeptidase M, leucine aminopeptidase). When human serum was incubated with neuropeptide Y or peptide YY at micro- and nanomolar concentrations, Tyr-Pro was detected as a metabolite of both peptides. Formation of Tyr-Pro in serum was blocked in the presence of Lys-pyrrolidine and diprotin A (Ile-Pro-Ile), specific, competitive inhibitors of dipeptidyl peptidase IV. Incubation of neuropeptide Y or peptide YY with immunocytochemically defined, cultivated endothelial cells from human umbilical cord also yielded Tyr-Pro. Dipeptidyl peptidase IV could be immunostained on most endothelial cells by a specific antibody. We suggest that dipeptidyl peptidase IV might be involved in the degradation of neuropeptide Y and peptide YY to N-terminal truncated neuropeptide Y(3-36) and peptide YY(3-36). Since specific binding to Y1, but not to Y2 subtype of neuropeptide Y/peptide YY receptors requires intact N- as well as C-termini of neuropeptide Y and peptide YY, removal of their amino-terminal dipeptides by dipeptidyl peptidase IV inactivates them for binding to one receptor subtype.

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Proline motifs in peptides and their biological processing.

Vanhoof G, Goossens F, De Meester I, Hendriks D, Scharpe S.

Department of Clinical Biochemistry, University of Antwerp, Wilrijk, Belgium.

Many biologically important peptide sequences contain proline. It confers unique conformational constraints on the peptide chain in that the side-chain is cyclized back onto the backbone amide position. Inside an alpha-helix the possibility of making hydrogen bonds to the preceding turn is lost and a kink will be introduced. The conformational restrictions imposed by proline motifs in a peptide chain appear to imply important structural or biological functions as can be deduced from their often remarkably high degree of conservation as found in many proteins and peptides, especially cytokines, growth factors, G-protein-coupled receptors, V3 loops of the HIV envelope glycoprotein gp 120, and neuro- and vasoactive peptides. Only a limited number of peptidases are known to be able to hydrolyze proline adjacent bonds. Their activity is influenced by the isomeric state (cis-trans) as well as the position of proline in the peptide chain. The three proline specific metallo-peptidases (aminopeptidase P, carboxypeptidase P and prolidase) are activated by Mn²⁺, whereas the three serine type peptidases cleaving a post proline bond (prolyl oligopeptidase, dipeptidyl peptidase IV, and prolylcarboxypeptidase) share the sequential order of the catalytic Ser-Asp-His triade, which differentiates them from the chymotrypsin (His-Asp-Ser) and subtilisin (Asp-His-Ser) families. An endo or... C terminal Pro-Pro bond and an endo pre-Pro peptide bond possess a high degree of resistance to any mammalian proteolytic enzyme.

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Primary structure of a novel human salivary acidic proline-rich protein.

Schlesinger DH, Hay DI, Schluckebier SK, Ahern JM.

Department of Medicine, New York University Medical Center, New York 10016.

Human salivary acidic proline-rich proteins (PRPs) form a significant fraction of the total salivary protein and fulfill several biologically important roles in the oral cavity. Five commonly occurring PRP polymorphisms, Db, Pa, PIF, Pr2 and Pr1, have been identified, their structures determined, and several uncommon polymorphisms (frequencies < 1:100) have been reported. Most PRPs occur as protein pairs, because of an unusual, limited but well-controlled post-translational cleavage. We now describe an additional uncommon polymorphism, found in the saliva of one of 127 individuals examined in a recent study, identified by high performance anion-exchange liquid chromatography. By analogy with previous terminology, we designate this protein pair as PRP-5, for the primary 150-residue polypeptide gene product, and PRP-6, for the secondary 106-residue cleavage product. Amino acid analysis of intact PRP-6 and sequence determination of PRP-6 chymotryptic peptides, residues 15-24 and 26-35, show a single difference in PRP-6, compared to the most similar, characterized PRP, PRP-4, in that residue 30 is histidine in PRP-6, rather than arginine as in PRP-4 and in all the other sequenced PRPs. This substitution may have implications for the resistance of this polymorphic variant to degradation by trypsin-like enzymes originating from the oral microflora.

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